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Neutrophil-to-high-density lipoprotein ratio: an independent predictor of infarct-related artery patency in patients with acute myocardial infarction

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ABSTRACT

Aims: The definition of an infarct-related artery (IRA) is a coronary artery occluded by a thrombus or atheroma that causes ischemia during acute myocardial infarction (AMI). Early patency of the IRA is the primary goal of treatment in patients with AMI. The neutrophil/ high-density lipoprotein cholesterol (HDL-C) ratio (NHR) has been recognized as a new inflammatory marker. We aimed to show the possible relationship between NHR and preprocedural IRA patency.

Methods: Four hundred patients were screened, and 318 were included in the study after exclusion criteria. IRA flow rate before the coronary procedure was determined according to the previously described thrombolysis in myocardial infarction (TIMI). TIMI current 0,1 and 2 patients were considered IRA non-patent, and TIMI-3 patients were considered IRA patent and were divided into two groups. Regression analysis was performed for possible parameters in predicting IRA patency, evaluated in univariable analysis, and those with p-value <0.05 were assessed in multivariable analysis.

Results: The mean age was 62.3±11.9 years, and 73.4% were male. In multivariable logistic regression analysis, high peak troponin (ng/ml) (p<0.001, OR: 0.936, 95% CIs: 0.910-0.962) and NHR (p= 0.020, OR: 0.043, 95% CIs: 0.003-0.603) levels were found to be independent predictors of patent IRA.

Conclusion: Our study investigated the relationship between IRA patency and NHR in AMI patients. The main finding of our research is that significantly higher NHR and peak troponin levels were associated with non-patent IRA patients and were independent predictors.

Keywords: Acute myocardial infarction, vascular patency, high-density lipoprotein, neutrophil

INTRODUCTION

Acute myocardial infarction (AMI) is a condition of myocardial ischemia resulting from the acute decrease in coronary artery blood flow after rupture or erosion of coronary atherosclerotic plaque. Despite modern fibrinolytic and early reperfusion treatment strategies, it is the leading cause of death in the world.[1] The definition of an infarct-related artery (IRA) is a coronary artery occluded by a thrombus or atheroma that causes ischemia during AMI.[2] Patients with ST-elevation myocardial infarction (STEMI) have transmural ischemia, and the IRA is usually occluded at admission, so early treatment strategies are of great importance. Non-ST-elevation myocardial infarction (NSTEMI) patients have subendocardial ischemia, and 30% of the IRA is occluded at admission.[3] Early provision of IRA patency has been identified as the primary goal in all treatment strategies in terms of improving prognosis. Improved ventricular performance and reduced in-hospital death rates are seen in IRA patent patients on admission.[4]

The pathophysiology of coronary artery disease (CAD) is quite complex. Inflammation, altered lipid metabolism, oxidative stress, and other processes are considered effective in pathophysiological processes. Inflammation plays an essential role in the pathogenesis of atherosclerosis and AMI.[5] The neutrophil/ high-density lipoprotein cholesterol (HDL-C) ratio (NHR) has been recognized as a new inflammatory marker. This is because neutrophils and HDL-C particles have opposing effects: while neutrophils play an active role in inflammation,[6] HDL-C has antioxidant and anti-inflammatory properties. HDL-C protects the endothelium against the effects of low-density lipoprotein cholesterol (LDL-C) and thus has an antioxidant and anti-inflammatory effect.[7] In previous

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studies, high NHR is associated with cardiovascular disease prognosis and severity. It is associated with prognosis in patients with STEMI and acute ischemic stroke.[8,9] It has also been an independent predictor of coronary artery disease severity.[10]

In our study, we aimed to show the possible relationship between NHR, this inflammatory marker is new and associated with cardiovascular disease prognosis and preprocedural IRA patency, an important prognostic indicator in outcomes such as ventricular performance and in-hospital mortality.

METHODS

The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-047). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our retrospective case-control study enrolled AMI patients who applied to our center between November 2022 and January 2023. Four hundred patients were analyzed, and 318 were included in the study after exclusion criteria. The diagnosis of AMI was made according to the criteria of the "Fourth Universal Myocardial Infarction Guidelines" published by the European Heart Association in 2018.[11] All patient data were obtained using the hospital's digital database. Exclusion criteria were; being under the age of 18, severe valve disease, active infection, acute liver/kidney failure, active cancer, history of inflammatory disease, receiving fibrinolytic therapy within 24 hours, and rheumatological disease.

NHR was obtained by dividing the neutrophil (10^3/ml) and serum HDL-C levels (mg/dl) received at admission. The modified Simpson method calculates the left ventricular ejection fraction (LVEF).

Coronary arteries were visualized using the standard Judkins technique. Angiographic images of the patients were obtained and evaluated via the hospital's digital PACS system. IRA was detected for each patient; patients with more than one IRA were not included in the study. Each coronary artery was visualized and evaluated in at least two planes. Two experienced cardiologists, unaware of patient groups, blindly evaluated coronary angiograms and coronary artery flow rates. Before percutaneous coronary intervention, thrombolysis in myocardial infarction (TIMI) flow grade was documented for each patient. IRA flow rate before the coronary procedure was determined according to the previously described TIMI.[12] TIMI current 0, 1 and 2 patients were considered IRA non-patent, TIMI-3 patients were considered IRA patent and were divided into two groups.[13]

Statistical Analysis

Statistical analyzes of the study were performed using SPSS 25.0 for Windows. Continuous variables were shown as mean±standard deviation. Categorical variables were given as numbers and percentages. The normal distribution of the data was evaluated with the Shapiro-Wilk test. We used Levene's test to determine the homogeneous distribution. The student-t test was used for normally distributed continuous variables fulfilling the parametric test conditions, and the Mann-Whitney U test was used to compare the variables that did not show the normal distribution and did not meet the parametric test conditions. Categorical variables were compared by χ^2 test. Receiver operating characteristic curve (ROC) analysis was used to define the optimum cut-off level of NHR and the area under the curve to estimate IRA patency. Regression analysis was performed for possible parameters in predicting IRA patency, evaluated in univariable analysis, and those with p-value <0.05 were evaluated in multivariable analysis. P<0.05 was considered to be statistically significant.

RESULTS

A total of 318 patients were included in the study, and they were divided into two groups IRA non-patent (n: 182) and IRA patent (n: 136). The mean age was 62.3±11.9 years, and 73.4% were male. Age was significantly higher in the IRA patent group (64.4±11.3 vs 60.8±12.1, p= 0.007). Hypertension history was more common in the IRA patent group (52.2% vs 40.1%, p= 0.032). Peak troponin value was significantly higher in the IRA non-patent group (14.7±10.1 vs. 6.9±8.2, p<0.001). No statistically significant difference was observed when troponin analysis was performed according to TIMI-0 vs. TIMI-1,2 subgroups in the non-patent group (15.08±10.2 vs. 13.1±10.0, p=0.198). Baseline clinical, laboratory, and angiographic characteristics between groups are shown in **Table 1**. A comparison of NHR in study groups is shown in **Figure 1**.

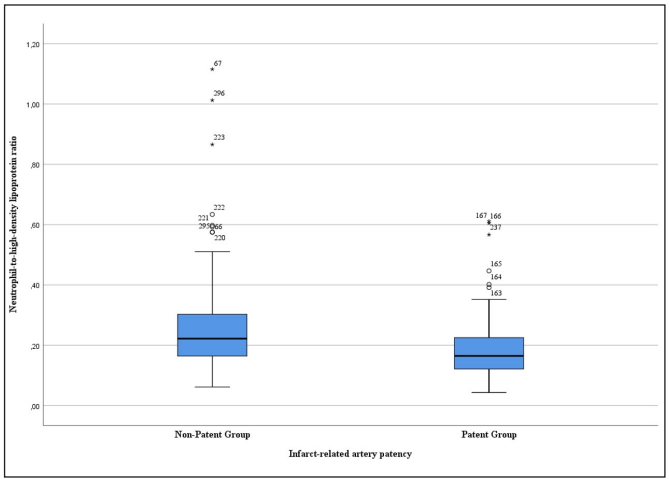

Figure 1. Comparison of NHR in study groups

Table 1. Baseline clinical, laboratory, and angiographic characteristics between groups

Variables	All patients, (n: 318)	IRA Non-patent Group, (n: 182)	IRA patent Group, (n: 136)	p
Sex, male n (%)	235 (73.4%)	139 (76.4%)	96 (70.6%)	0.245
Diabetes mellitus, n (%)	205 (64.5%)	59 (32.4%)	54 (39.7)	0.179
Hypertension, n (%)	174 (54.7%)	73 (40.1%)	71 (52.2%)	0.032
Previous history of CAD, n (%)	215 (67.6%)	51 (28.0%)	52 (38.2%)	0.054
Age, years	62.3±11.9	60.8±12.1	64.4±11.3	0.007
Serum glucose, mg/dl	151.8±72.2	155.1±73.0	147.3±71.2	0.339
Serum creatinine, mg/dl	0.92±0.34	0.91±0.31	0.92±0.36	0.751
Urea, mg/dl	35.7±17.0	35.5±17.7	36.0±16.2	0.792
Total cholesterol, mg/dl	183.0±48.0	179.3±45.6	188.0±50.8	0.113
LDL-cholesterol, mg/dl	127.0±43.6	126.3±41.9	128.0±45.9	0.740
HDL-cholesterol, mg/dl	39.6±9.9	39.3±10.1	40.0±9.8	0.504
Triglyceride, mg/dl	139.8±91.6	132.7±86.4	149.3±97.5	0.109
Sodium, mmol/L	137.3±2.9	137.0±3.0	137.7±2.7	0.036
Potassium, mmol/L	4.2±0.4	4.2±0.4	4.2±0.4	0.610
White blood cell count, 103/ml	11.22±3.83	12.25±4.03	9.84±3.07	<0.001
Hemoglobin, g/dl	13.6±1.9	13.7±1.9	13.5±1.9	0.231
Platelet count, 103/ml	256.6±74.4	259.0±78.6	253.3±68.6	0.506
Neutrophil count, 103/ml	8.35±3.79	9.36±3.98	7.00±3.05	<0.001
Lymphocyte count, 103/ml	1.97±0.90	1.97±0.97	1.98±0.80	0.943
Peak troponin, ng/ml	11.4±10.1	14.7±10.1	6.9±8.2	<0.001
NHR	0.225±0.130	0.254±0.145	0.186±0.096	<0.001
Left ventricular EF, (%)	47.2±10.7	45.3±9.8	49.8±11.5	<0.001
Infarct-related artery, n (%)				
Left anterior descending artery	126 (39.6%)	76 (41.8%)	50 (36.8)	0.368
Circumflex artery	80 (25.2%)	44 (24.2%)	36 (26.5%)	0.641
Right coronary artery	112 (35.2%)	62 (34.1%)	50 (36.8%)	0.618

CAD: coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, NHR: Neutrophil to High-density lipoprotein ratio, EF: ejection fraction

In multivariable logistic regression analysis, high peak troponin (ng/ml) (p<0.001, Odds Ratio (OR): 0.936, 95% Confidence Intervals (CIs): 0.910-0.962) and NHR (p= 0.020, OR: 0.043, 95% CIs: 0.003-0.603) levels were found to be independent predictors of patent IRA. Univariable and multivariable regression analyses of potential predictive factors in determining IRA patency are shown in Table 2.

Table 2. Univariable and multivariable logistic regression analysis showing the independent predictors for the IRA patency

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Hypertension	0.613 (0.392-0.960)	0.033	0.738 (0.438-1.243)	0.254
Age, years	1.027 (1.007-1.047)	0.008	1.023 (1.000-1.046)	0.053
Sodium	1.087 (1.005-1.176)	0.037	1.065 (0.976-1.162)	0.159
Peak troponin	0.920 (0.897-0.943)	<0.001	0.936 (0.910-0.962)	<0.001
NHR	0.003 (0.000-0.037)	<0.001	0.043 (0.003-0.603)	0.020
LVEF, (%)	1.041 (1.018-1.064)	<0.001	1.020 (0.996-1.046)	0.106

OR: Odds ratio, CI: confidence interval NHR: Neutrophil to HDL ratio, LVEF: left ventricular ejection fraction

As revealed by the ROC curve analysis, the cut-off value of 0.192 for NHR predicted the non-patent IRA with a sensitivity of 61.5% and specificity of 61.8% (AUC: 0.680; CIs: 0.621-0.740; p<0.001; Figure 2).

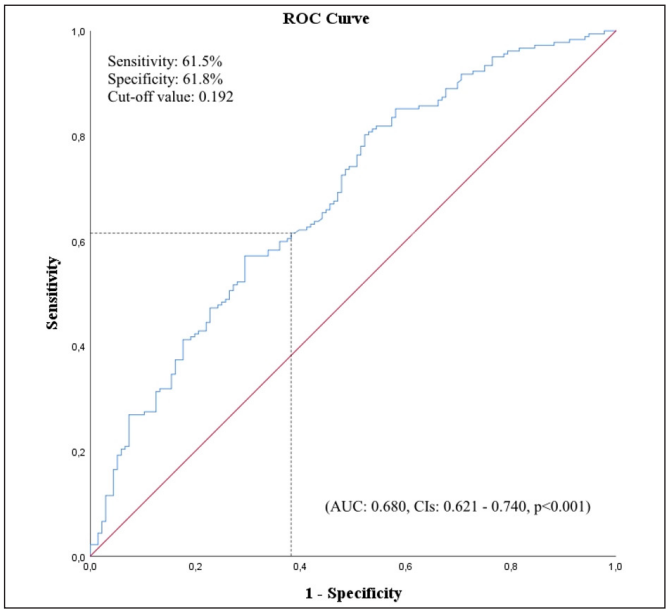

Figure 2. Receiver operating characteristics (ROC) curves of NHR associated with IRA patency

DISCUSSION

Our study investigated the relationship between IRA patency and NHR in AMI patients. The main finding of our research is that significantly higher NHR and peak troponin levels were associated with non-patent IRA patients and were independent predictors.

Troponin is a contractile protein involved in myocardial contraction. It is secreted from ischemic tissue when the coronary artery is wholly or partially occluded by atheroma or thrombus, and myocardial blood flow decreases. It has an essential place in the diagnosis of AMI. Troponin levels are significantly higher in IRA non-patent patients.[14] Although troponin values were significantly higher in the non-patent group, we found high troponin values to be an independent predictor of IRA patency.

Our study found a significantly higher age in the IRA-patent group. No studies are comparing IRA patency with age in AMI patients. A previous study also reported that preprocedural IRA patency in STEMI patients was more common in older individuals, and advanced age was an independent predictor.[15] This is consistent with the findings of our study. However, the regression analysis did not detect age as an independent predictor.

Early patency of the IRA is the primary goal of treatment in patients with AMI. Non-patent IRA at admission has been associated with poor clinical outcomes. Early provision of IRA patency is essential in preserving ventricular performance and reducing the risk of mechanical and fatal arrhythmias, especially in STEMI patients.[16] On the other hand, it was observed that IRA was non-patent at the rate of 30% at admission in NSTEMI patients.[3] IRA patency is decided according to the TIMI flow rate. TIMI-3 flow rate monitoring at admission has been associated with good clinical outcomes.[13] Stone et al.[17] found that LVEF, an important prognostic marker, was preserved in patients with IRA flow TIMI-3 and achieved better results than those with TIMI-0, 1 and 2. In our study, LVEF, an important prognostic marker in AMI patients, was significantly lower in the IRA non-patent group. Restoring early IRA patency offers the advantage of reduced infarct area, in-hospital mortality, and arrhythmia complications.[18] IRA patency in admission is also an important indicator of post-procedural patency. Failure to obtain IRA patency angiographically; a post-procedural IRA non-patent is defined as no-reflow and is a known predictor of poor prognosis.[19] For all these reasons, early estimation and restoration of IRA patency are critical in terms of prognosis. In previous studies, researchers investigated the role of different markers in predicting IRA patency at admission. In their study, Doğan et al.[20] reported that neutrophil-lymphocyte ratio, another inflammatory marker, predicts IRA patency in STEMI patients. Another study examined hematological parameters in STEMI patients who underwent primary angioplasty. The number of white blood cells (WBC), which plays a vital role in inflammation, was associated with IRA patency.[21] Our findings are similar to non-patent IRA patients' significantly higher WBC count. When the results of these studies are evaluated, it may be said that the underlying mechanism of IRA patency is inflammation.

Inflammation is essential in developing atherosclerotic plaque formation and initiating and progressing intracoronary thrombus formation in AMI.[22] Neutrophils play a crucial role in the AMI process. It is known that atherogenesis, the primary mechanism of coronary artery disease, and plaque erosion, one of the initial pathophysiological stages of AMI, are involved. After plaque erosion and rupture, the subendothelial tissue comes into contact with blood, neutrophils, and platelets rapidly collect in the lesion area, activating the coagulation cascade, and a thrombus forms.[23,24]

HDL-C has anti-inflammatory, antioxidant, antithrombotic, anti-atherosclerotic, and reverse cholesterol transport effects.[25] Atherosclerosis and stable coronary artery disease, which constitute the previous mechanism in AMI, are closely related to inflammation. Özkan et al.[26] reported in their study that the Systemic Immune-Inflammation Index predicted coronary artery severity. Because neutrophils are a cell group that has an active role in inflammation and HDL-C has anti-inflammatory effects, we can accept NHR as a new inflammatory marker that more strongly indicates inflammation. NHR, an indicator of inflammatory cells and lipid cholesterol, could be a new indicator showing inflammatory and lipid metabolism together. It has been demonstrated that NHR indicates prognosis as an inflammatory marker in patients with ischemic stroke and patients with STEMI.[8,9] NHR, a combined parameter over a single parameter, may be more comprehensive and reliable.

In light of the results of our study, we showed that NHR, an inexpensive and easily calculable biomarker, can be an independent predictor of preprocedural IRA patency status in patients presenting with AMI.

This study has some limitations. The first is that it is a single-center and retrospective study. We could not examine inflammation markers, CRP, and cytokines as they have not been routinely studied. Third, we only calculated NHR at admission and did not evaluate follow-up values. Fourth, since door-to-balloon time is not routinely recorded in AMI patients in our

center, this condition, which impacts thrombotic/antithrombotic mechanisms, could not be evaluated in our study. However, the findings of our study may be valuable for future studies and can be used in risk classification.

CONCLUSIONS

In conclusion, in this study, we found that high NHR levels were an independent predictor of non-patent IRA at presentation. Based on our findings, using NHR to estimate IRA patency in daily clinical practice may be valuable in risk and prognosis assessment. More extensive and more comprehensive studies are needed on this useful inflammatory biomarker.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-047).

Informed Consent: Because the study was designed retrospectively, no written informed consent from was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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